APPENDIX 1

Genes VII

Benjamin Lewin

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS
Great Clarendon Street, Oxford OX2 6DP
Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide in
Oxford New York
Athens Auckland Bangkok Bogotá Buenos Aires Calcutta
Cape Town Chennai Dar es Salaam Delhi Florence Hong Kong Istanbul
Karachi Kuala Lumpur Madrid Melbourne Mexico City Mumbai
Nairobi Paris São Paulo Singapore Taipei Tokyo Toronto Warsaw
with associated companies in Berlin Ibadan

Oxford is a registered trade mark of Oxford University Press
in the UK and in certain other countries

Published in the United States
by Oxford University Press Inc., New York

First published 2000

A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
(Data applied for)

ISBN 0–19–879276–X (Hbk)

Typeset by J&L Composition Ltd, Filey, North Yorkshire
Printed in The United States of America

operator, and is therefore constitutive like the *lacI*⁻ alleles. Because the *lacI*⁻ type of mutation inactivates the repressor, it is recessive to the wild type. However, the *–d* notation indicates that this variant of the negative type is dominant when paired with a wild-type allele. Such mutations are said to be *trans*-dominant; they are also called dominant negatives.

The reason for the dominance is that the *lacI*$^{-d}$ allele produces a "bad" subunit, which is not only itself unable to bind to operator DNA, but is also able as part of a tetramer to prevent any "good" subunits from binding. This demonstrates that the repressor tetramer as a whole, rather than the individual monomer, is needed to achieve repression. The poisoning effect also can be

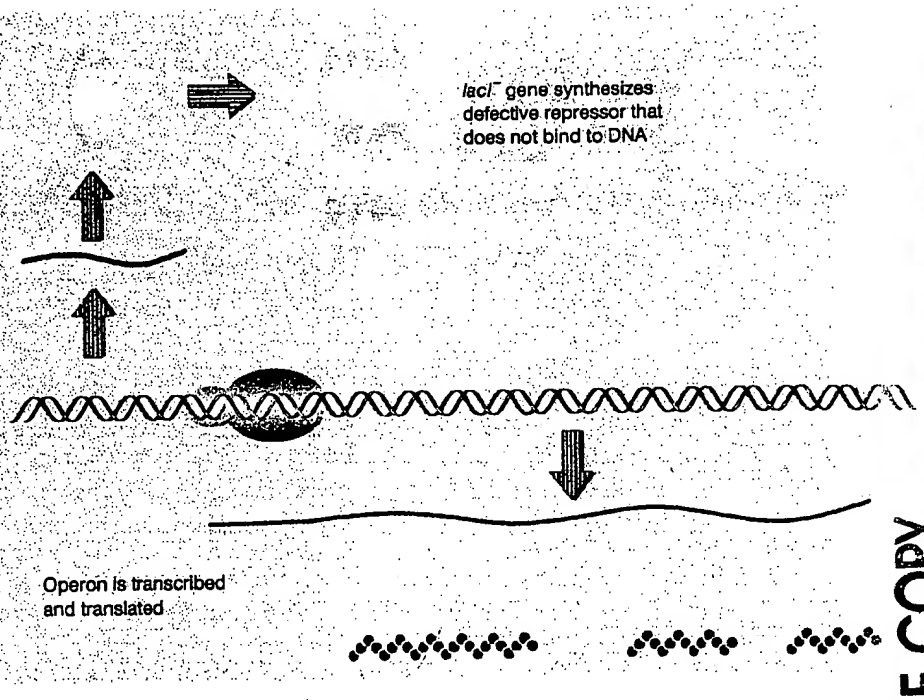

Figure 10.8 Mutations that inactivate the *lacI* gene cause the operon to be constitutively expressed, because the mutant repressor protein cannot bind to the operator.

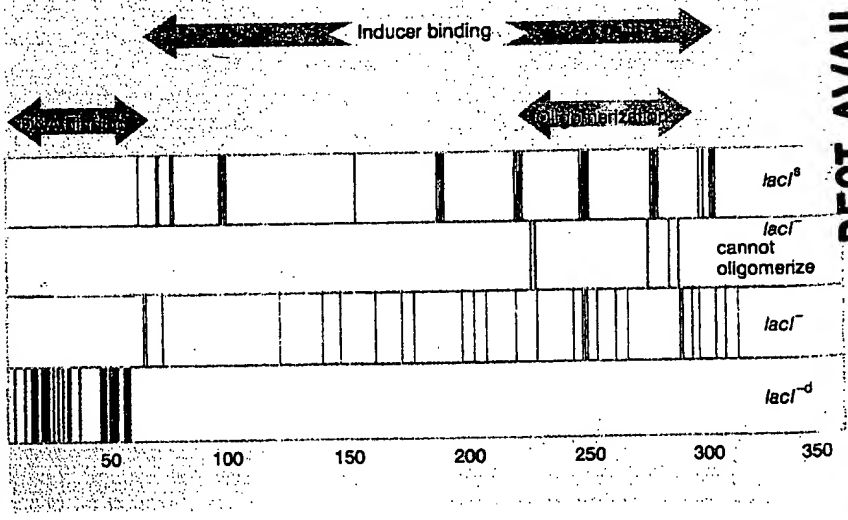

Figure 10.9 Mutations map the regions of the *lacI* gene responsible for different functions. The DNA-binding domain is identified by *lacI*$^{-d}$ mutations at the N-terminal region; *lacI*⁻ mutations unable to form tetramers are located between residues 220–280; other *lacI*⁻ mutations occur throughout the gene; *lacI*^{s} mutations occur in regularly spaced clusters between residues 62–300.

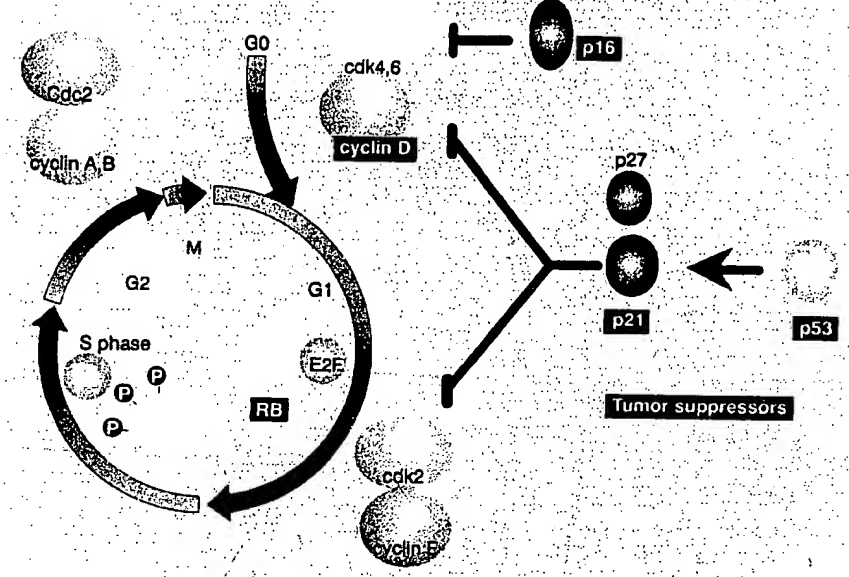

Figure 28.23
Several components concerned with G0/G1 or G1/S cycle control are found as tumor suppressors.

Tumor suppressor p53 suppresses growth or triggers apoptosis

The most important tumor suppressor is p53 (named for its molecular size). More than half of all human cancers either have lost p53 protein or have mutations in the gene. p53 is a nuclear phosphoprotein. It was originally discovered in SV40-transformed cells, where it is associated with T antigen. A large increase in the amount of p53 protein is found in many transformed cells or lines derived from tumors. In early experiments, the introduction of cloned p53 was found to immortalize cells. These experiments caused p53 to be classified as an oncogene, with the usual trait of dominant gain-of-function.

But all the transforming forms of p53 turned out to be mutant forms of the protein! They fall into the category of dominant negative mutants, which function by overwhelming the wild-type protein and preventing it from functioning. The most common form of a dominant negative mutant is one that forms a heteromeric protein containing both mutant and wild-type subunits, in which the wild-type subunits are unable to function. p53 probably exists as a tetramer. When mutant and wild-type subunits of p53 associate, the tetramer takes up the mutant conformation.

Figure 28.24 shows that the same phenotype is produced either by the deletion of both alleles or by a missense point mutation in one allele that produces a dominant negative subunit. Both situations are found in human cancers. Mutations in p53 accumulate in many types of human cancer, probably because loss of p53 provides a growth advantage to cells; that is, wild-type p53 restrains growth. The diversity of these cancers suggests that p53 is not involved in a tissue-specific event, but in some general and rather common control of cell proliferation; and the loss of this control may be a secondary event that occurs to assist the growth of many tumors. Mutant p53 cells also have an increased